Comparison of the Efficacy and Safety of Early Rule Out Pathways for Acute Myocardial Infarction

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Abstract

Background —High-sensitivity cardiac troponin assays enable myocardial infarction to be ruled out earlier, but the optimal approach is uncertain. We compared the European Society of Cardiology (ESC) rule-out pathway, with a pathway that incorporates lower cardiac troponin concentrations to risk stratify patients.

Methods —Patients with suspected acute coronary syndrome (n=1,218) underwent high-sensitivity cardiac troponin I measurement at presentation, 3 and 6 or 12 hours. We compared the ESC pathway (<99th centile at presentation, or at 3 hours if symptoms <6 hours) with a pathway developed in the *High-S*ensitivity *T*roponin in the *E*valuation of patients with *A*cute *C*oronary *S*yndrome (High-STEACS) study population (<5 ng/L at presentation, or change <3 ng/L and <99th centile at 3 hours). The primary outcome was a comparison of the negative predictive value (NPV) of both pathways for index type 1 myocardial infarction, or type 1 myocardial infarction or cardiac death at 30 days. We evaluated the primary outcome in pre-specified subgroups stratified by age, gender, time of symptom onset and known ischaemic heart disease.

Results —The primary outcome occurred in 15.7% (191/1,218) patients. In those <99th centile at presentation, the ESC pathway ruled out myocardial infarction in 28.1% (342/1,218) and 78.9% (961/1,218) at presentation and 3 hours respectively, missing 18 index and two 30-day events (NPV 97.9%, 95% confidence intervals [CI] 96.9-98.7%). The High-STEACS pathway ruled out 40.7% (496/1,218) and 74.2% (904/1,218) at presentation and 3 hours, missing two index and two 30-day events (NPV 99.5%, 95% CI 99.0-99.9%; P<0.001 for comparison). The NPV of the High-STEACS pathway was greater than the ESC pathway overall (P<0.001), and in all subgroups including those presenting early or known to have ischaemic heart disease.

Conclusions—Use of the High-STEACS pathway incorporating low high-sensitivity cardiac troponin concentrations rules out myocardial infarction in more patients at presentation and misses 5-fold fewer index myocardial infarctions than guideline approved pathways based exclusively on the 99th centile.

Clinical Trial Registration—https://clinicaltrials.gov Identifier: NCT:01852123

Key-words: acute coronary syndrome; acute myocardial infarction; troponin; biomarker; high-sensitivity assay

Clinical Perspective

What is new?

- The European Society of Cardiology (ESC) recommend high-sensitivity cardiac troponin assays to rule out myocardial infarction using a three-hour pathway based on the 99th centile.
- In this study of 1,218 patients, the ESC pathway had a negative predictive value (NPV) of 97.9% missing 18 index and two recurrent myocardial infarction.
- We propose a new pathway using a high-sensitivity cardiac troponin I assay that incorporates a risk stratification threshold of <5 ng/L at presentation, and no change (<3 ng/L) at three hours.
- This pathway had a higher NPV than the ESC pathway at 99.5%, missing two index and two recurrent events.

What are the clinical implications?

- The 99th centile is not the optimal threshold to rule out myocardial infarction at presentation or at three hours, and pathways based exclusively on this threshold may miss patients with myocardial infarction.
- Use of the High-STEACS pathway, incorporating a risk stratification threshold at presentation and recognising small but important changes in cardiac troponin within the normal reference range on serial testing, will minimise the risk of missed events.
- Importantly, the use of risk stratification thresholds identifies more patients as low risk at presentation, permitting a higher proportion of patients to be safely discharged.

Introduction

Chest pain is a frequent presenting symptom in patients attending the Emergency Department, with significant resource implications for healthcare providers.[1] Whilst the majority of patients with chest pain do not have an acute myocardial infarction[2], prompt and accurate exclusion of this diagnosis remains challenging in clinical practice, and often results in unnecessary hospital admission.[3-5] Guidelines from the European Society of Cardiology (ESC) support the use of high-sensitivity cardiac troponins and earlier testing to rule out myocardial infarction where concentrations are <99th centile upper reference limit (URL) at presentation in those patients with symptoms for more than 6 hours, and at 3 hours in the remainder.[6] A similar approach was recommended by the National Institute of Clinical Health and Excellence (NICE), although concerns were raised about the generalisability of the studies evaluating the effectiveness of this approach.[7]

Recent studies have demonstrated that very low cardiac troponin concentrations can help to further risk stratify patients.[8-22] As such, the latest European guidelines include an additional one hour pathway incorporating lower thresholds of cardiac troponin for risk stratification.[6] We recently demonstrated in consecutive patients with suspected acute coronary syndrome that a cardiac troponin concentration <5 ng/L at presentation had a negative predictive value of 99.6% [95%CI 99.3–99.8] for myocardial infarction during the index presentation, or myocardial infarction or cardiac death at 30 days. Furthermore, patients with cardiac troponin concentrations <5 ng/L had very low rates of adverse cardiac events at one year.[14]

Whilst it is clear that high-sensitivity cardiac troponins enable myocardial infarction to be ruled out earlier, the optimal approach is uncertain. As such, we compared the safety and

efficacy of the ESC pathway based on the 99th centile alone, with our clinical pathway incorporating low cardiac troponin concentrations to risk stratify patients.

Methods

Study population

Patients with suspected acute coronary syndrome were recruited from the Emergency Department of the Royal Infirmary of Edinburgh, a tertiary care hospital in Scotland, between 1st June 2013 and 31st September 2015 into a sub-study of the *High-S*ensitivity *T*roponin in the *E*valuation of patients with *A*cute *C*oronary *S*yndrome (High-STEACS) trial. All patients in whom the attending clinician requested cardiac troponin for suspected acute coronary syndrome were eligible for inclusion. We did not enrol patients with ST-segment elevation myocardial infarction, those who were unable to provide consent, or those from outside our region to ensure complete follow up. Blood samples were obtained at presentation and at 6-12 hours for high-sensitivity cardiac troponin testing as part of routine clinical care. Patients provided written informed consent for additional sampling at 3 hours with the results of testing at this time-point not used to guide patient care. This pre-specified analysis was restricted to those patients where serial samples were available (Figure S1). This clinical trial was registered (NCT:01852123), approved by the national research ethics committee, and conducted in accordance with the Declaration of Helsinki.

High-sensitivity cardiac troponin I assay

The Abbott ARCHITECT$_{STAT}$ high-sensitive cardiac troponin I assay (Abbott Laboratories, Abbott Park, IL) is a two-step chemo-luminescent assay with a limit of detection of 1.2 ng/L and coefficient of variation of less than 10% at 6 ng/L.[23] This assay performance has been

independently validated across multiple centres under routine laboratory working conditions, with a reported inter-laboratory coefficient of variation of 12.6% at 3.5 ng/L across 33 instruments.[14] The upper reference limit 99th centiles were determined in 4,590 samples from healthy individuals as 16 ng/L for women and 34 ng/L in men[10], and from 10th December 2013 onwards these thresholds were used in clinical practice.

Baseline characteristics

Patient baseline characteristics, including chest pain characteristics, onset of symptoms, prior medical history, cardiovascular risk factors, medication, and clinical observations, in addition to investigations including serial 12-lead electrocardiography and cardiac imaging, were obtained from a dedicated case record form, patient questionnaire and the electronic patient record (TrakCare, InterSystems, Cambridge, MA). Hyperlipidaemia or hypertension were defined as a history of the condition, or by the use of lipid-lowering or anti-hypertensive therapies, respectively. Ischaemic heart disease was defined as a history of angina, prior myocardial infarction or prior coronary revascularization.

Diagnostic adjudication

The final diagnosis was adjudicated for all patients by two independent physicians (AC/AA), with consensus from a third physician (JA/NM) where there was discrepancy following review of all clinical information, both non-invasive and invasive investigations and outcomes from presentation to 30 days. Patients were classified as having type 1 myocardial infarction, type 2 myocardial infarction or myocardial injury in accordance with the third universal definition of myocardial infarction as previously reported.[6,14] Any cardiac troponin I concentration above the sex-specific 99th centile upper reference limit was considered evidence of myocardial necrosis. Type 1 myocardial infarction was defined as myocardial necrosis in the context of a presentation

with symptoms suggestive of acute coronary syndrome or evidence of myocardial ischemia. Patients with symptoms or signs of myocardial ischemia due to increased oxygen demand or decreased supply (e.g. tachyarrhythmia, hypotension or anaemia) secondary to an alternative pathology and myocardial necrosis were classified as type 2 myocardial infarction. Myocardial injury was defined as evidence of myocardial necrosis in the absence of any clinical features of myocardial ischaemia. Agreement for a diagnosis of type 1 myocardial infarction was very good (κ= 0.82, 95%CI 0.75-0.89).

Clinical outcomes

The primary outcome was a composite of index type 1 myocardial infarction, or type 1 myocardial infarction or cardiac death at 30 days. We used regional and national registries in addition to individual patient follow up at 30 days to ensure follow up was complete for the entire study population. All subsequent events were adjudicated using the same approach as for the index presentation. TrakCare software application (InterSystems Corporation, Cambridge, MA, USA) is a regional electronic patient record system, which provides data on all hospital admissions to both tertiary or secondary care hospitals in the southeast of Scotland. All in-hospital and community deaths are recorded in a comprehensive national database, the General Register of Scotland. Cardiac death was defined as any death due to myocardial infarction, arrhythmia or heart failure.

Clinical pathways

We compared the safety and efficacy of two pathways to rule out the composite outcome of index myocardial infarction, and myocardial infarction or cardiac death at 30 days (Figure 1). The ESC pathway rules out myocardial infarction where cardiac troponin concentrations are <99th centile at presentation in patients with symptoms for more than 6 hours. In patients with

symptoms for less 6 hours, a second troponin measurement is performed 3 hours from presentation, with myocardial infarction ruled out if cardiac troponin remains <99th centile or is >99th centile without a significant change in concentration.[6] Previously published guidance from the ESC Working Group on Acute Cardiac Care recommends use of a change in cardiac troponin concentration >50% of the 99th centile upper reference limit at 3 hours.[24]

We compared the ESC pathway to the High-STEACS pathway, based on our previous observations, that utilises a risk stratification threshold of 5 ng/L at presentation.[14,25] This threshold has since been externally validated in separate populations, with a recent a multi-centre study across five independent cohorts finding a troponin concentration of <5 ng/L had a negative predictive value of 99.2% [95%CI 98.8-99.5%].[15] In our pathway, patients with cardiac troponin concentrations <5 ng/L at presentation are considered low risk and myocardial infarction is ruled out without further testing, unless they present early with symptom onset <2 hours from presentation where cardiac troponin is retested 3 hours after presentation.[14] Patients with cardiac troponin concentrations ≥5 ng/L at presentation are retested at 3 hours. Myocardial infarction is ruled out at 3 hours if cardiac troponin concentrations are unchanged and remain <99th centile on retesting. A change in cardiac troponin concentration was defined as an increase or decrease ≥3 ng/L at 3 hours, as this is the lowest measurable concentration within the normal reference range that exceeds analytical variation of the assay.[26] This change in cardiac troponin concentration was internally and externally validated, using data from the APACE cohort (Table S1).

Statistical analysis

Baseline characteristics are summarised as mean (standard deviation, SD) or median (inter-quartile range, IQR) as appropriate. Patients with maximal cardiac troponin concentrations ≤99th centile were compared with those >99th centile using a chi-square test or Wilcoxon rank sum test.

The primary outcome was the negative predictive value (NPV) of each pathway, using the composite endpoint of index type 1 myocardial infarction, or subsequent type 1 myocardial infarction or cardiac death at 30 days. As we estimated the NPV would approach 100%, we used a Bayesian approach with a Jeffrey's prior (beta distribution with both shape parameters equal to 0.5) as this is more robust when confidence intervals approach 0 or 1.[27] We derived a weighted generalised score statistic to compare the NPV of the ESC and the High-STEACS pathway, as previously described.[28] We evaluated the NPV in pre-specified subgroups stratified by time of symptom onset (<3, <6 or ≥6 hours), age (<65 or ≥65 years), sex, and history of ischaemic heart disease. We determined absolute (hs-TnI$_{3hr}$ – hs-TnI$_{0hr}$) and relative ([(hs-TnI$_{3hr}$ – hs-TnI$_{0hr}$) / hs-TnI$_{0hr}$] x 100) change in cardiac troponin concentration from presentation to 3 hours, and determined sensitivity, specificity and positive predictive value (PPV) with 95% confidence intervals (CI) using a Bayesian approach as per the NPV. In a sensitivity analysis, we evaluated the NPV for a primary outcome encompassing type 1 or type 2 myocardial infarction, or myocardial injury, or myocardial infarction or cardiac death at 30 days. To ensure our findings were generalizable to those centers that do not apply sex-specific diagnostic thresholds, we evaluated the performance of both pathways using a single 99th centile upper reference limit for men and women of 26 ng/L. A further sensitivity analysis evaluated the NPV in patients without evidence of myocardial ischaemia (defined as ≥2mm ST-segment depression or new T-wave inversion) on the presenting electrocardiogram, who were considered intermediate or low risk with a GRACE score of <140.[6] We evaluated pathway efficacy by determining the number of patients ruled out at 0 and 3 hours as a proportion of the total study population, with comparison by McNemar's test for paired proportions. A two-sided P<0.05 was considered statistically significant. All analyses were performed using R (Version 3.2.2).

Results

We identified 1,218 patients with suspected acute coronary syndrome who met our inclusion and exclusion criteria (62.4±14.1 years, 61% male; Table 1, Figure S1). The adjudicated diagnosis was type 1 myocardial infarction in 15.5% (189/1,218), type 2 myocardial infarction in 5.5% (67/1,218) and myocardial injury in 2.1% (26/1,218). There were six subsequent type 1 myocardial infarcts and six cardiac deaths at 30 days. At presentation, 216 patients had troponin concentrations >99th centile with 11.9% (145/1,218) type 1 and 3.8% (46/1,218) type 2 myocardial infarction, and 2.1% (25/1,218) patients with myocardial injury.

ESC pathway

The ESC pathway ruled out 28.1% (342/1,218) of patients at presentation and 78.9% (961/1,218) of all patients by 3 hours. However, this approach missed 18 index type 1 myocardial infarctions (four on presentation, fourteen at three hours) and two subsequent myocardial infarctions within 30 days for an overall NPV of 97.9% [95% CI, 96.9-98.7%; Table 2, Figure 2]. The sensitivity of this pathway is 89.3% [95% CI, 84.9-93.5%], and a summary of the missed events is provided in Table S2.

High-STEACS pathway

In comparison, the High-STEACS pathway ruled out 40.7% (496/1,218) of patients at presentation, and 74.2% (904/1,218) of all patients by 3 hours. There were two missed index type 1 myocardial infarction (none at presentation, two at three hours) and two recurrent events for an overall NPV of 99.5% [95% CI, 99.0-99.9]; Table 2, Figure 2). All events missed by the High-STEACS pathway were also missed by the ESC pathway. The sensitivity of the High-STEACS pathway was 97.7% [95% CI, 95.5-99.5%] and a summary of missed events is provided in Table S3.

The High-STEACS pathway identifies more patients potentially suitable for discharge at presentation following a single cardiac troponin measurement compared to the ESC pathway (40.7% [95% CI, 38.0-43.5%] *versus* 28.1% [95% CI, 25.6-30.7%] respectively, P<0.001; ***Figure 1***). At three hours, the High-STEACS pathway ruled our fewer patients than the ESC pathway (74.2% [95% CI, 71.7-76.6%] *versus* 78.9% [95% CI, 76.5-81.1%], P<0.001). In the 57 patients ruled out at three hours by the ESC pathway but not the High-STEACS pathway, there were 13 missed index myocardial infarction (22.8%).

The NPV of the High-STEACS pathway was greater than the ESC pathway overall (99.5% [95%CI 99.0-99.9] *versus* (97.9% [95%CI 96.9-98.9%]; P<0.001), and for all pre-specified subgroups (Table 2, Figure 2). In the subgroup of patients who presented within three hours of symptom onset there were more false negatives and the NPV was lower with the ESC pathway (9 false negatives, NPV 97.8% [95% CI, 96.2-99.0%]) than with the High-STEACS pathway (1 false negative, NPV 99.6% [95% CI, 98.8-100.0%]). Similar differences were apparent in those patients presenting within six hours of symptom onset (ESC *versus* High-STEACS, NPV 97.5% [95% CI, 96.1-98.6%] *versus* 99.6% [95% CI, 98.9-99.9%]). In men, the NPV of the ESC pathway was lower than the High-STEACS pathway (97.4% [95% CI, 96.0-98.5%] *versus* 99.4% [95% CI, 98.5-99.8%]), although both pathways performed similarly in women. The lowest NPV for both the ESC and the High-STEACS pathway was in the subgroup of patients known to have ischaemic heart disease (95.8% [95% CI, 93.6-97.6%] and 98.7% [95% CI, 97.4-99.6%] respectively).

In patients with an index type 1 myocardial infarction missed by the ESC pathway, the median change in cardiac troponin concentration between presentation and 3 hours was 5.5 ng/L (inter-quartile range [IQR] 4.0-13.3 ng/L). The majority of these patients (16/18) were not ruled

out at 3 hours by the High-STEACS pathway as the change in cardiac troponin concentration was ≥3 ng/L (Table S4***)*** and further testing at 6 hours is recommended. In an external validation cohort of 2,533 patients with suspected acute coronary syndrome (Table S1), a change in cardiac troponin concentration <3 ng/L at 3 hours ruled out 69.9% of those patients who required retesting (514/735), and missed no patients with an index diagnosis of type 1 myocardial infarction (Table S5).

The specificity and PPV of the ESC pathway was greater than the High-STEACS pathway at three hours (specificity 91.6% [95% CI, 89.9-93.3] and PPV 66.5% [95% CI, 60.6-72.1] *versus* specificity 87.6% [95% CI, 85.6-89.6%] and PPV 59.5% [95% CI, 54.1-64.9%], Table 2). However, the overall specificity and PPV of the High-STEACS pathway was comparable when patients requiring additional testing at 6 hours were included (specificity 91.4% [95% CI, 89.7-93.1%] and PPV 67.9% [95% CI, 62.3-73.3%], Table S6).

Sensitivity analyses

In a sensitivity analysis, we evaluated both pathways using a single 99th centile upper reference limit for men and women of 26 ng/L. The performance of both pathways was similar, with a NPV of 97.7% [95% CI, 96.6-98.5%] for the ESC pathway (20 missed index type 1 myocardial infarction and two missed events at 30 days), and 99.4% [95% CI, 98.8-99.8%] for the High-STEACS pathway (three missed index type 1 myocardial infarction and two missed 30 day events). The ESC pathway missed a similar proportion of men and women (10 men, 12 women).

We performed a further sensitivity analysis excluding patients with evidence of myocardial ischaemia on the electrocardiogram or with a GRACE score >140 (n=224), of whom 71 patients had an index type 1 myocardial infarction. The diagnostic accuracy of both pathways improved. The ESC pathway still missed 13 index and one subsequent event (NPV 98.3% [95%

CI, 97.3-99.0%]), whereas the High-STEACS pathway missed only one index and one subsequent event (NPV 99.7% [95% CI, 99.2-99.9%] P<0.001).

We evaluated the diagnostic performance of both pathways for a composite endpoint incorporating an index diagnosis of type 1 or type 2 myocardial infarction, or myocardial injury, or myocardial infarction or cardiac death at 30 days. The High-STEACS pathway missed an additional five events, whilst the ESC pathway missed an additional nine events (High-STEACS NPV 99.0% [95% CI, 98.2-99.5%], nine false negatives; two index type 1 and five index type 2 myocardial infarction, two type 1 myocardial infarction at 30 days, *versus* ESC NPV 96.9% [95% CI, 95.8-97.9%], 29 false negatives; 18 index type 1 and nine index type 2 myocardial infarction, two type 1 myocardial infarction at 30 days, respectively).

Discussion

In patients with suspected acute coronary syndrome, we describe a clinical pathway utilising low cardiac troponin concentrations within the reference range to risk stratify patients. This approach identifies more patients as low risk at presentation, and has a better overall negative predictive value than guideline approved pathways based solely on the 99th centile. Implementation of this pathway has the potential to improve the efficiency and safety of early rule-out approaches for patients with suspected acute coronary syndrome.

We make a number of important and clinically relevant observations. First, we demonstrate the High-STEACS pathway misses fewer patients with an index diagnosis of myocardial infarction, or myocardial infarction or cardiac death events at 30 days than the pathway approved by the European Society of Cardiology (4 missed events *versus* 20 missed events). Second, the negative predictive value of our pathway is 99.5% and better than the

existing ESC pathway across all pre-specified subgroups. In particular, the ESC pathway was less effective in men, those with a history of ischaemic heart disease, and those presenting early after the onset of symptoms. Third, in patients without an elevated troponin concentration at presentation, the High-STEACS pathway identified half as low risk with a single measurement, compared to a third identified using the established pathway. This is despite being safer, and missing fewer patients with an index myocardial infarction.

The European Society of Cardiology guideline recommends the use of high-sensitivity cardiac troponin assays, and their central algorithm advises the 99th centile be used as the threshold to rule in and rule out myocardial infarction at presentation and at three hours.[6] However, the 99th centile may not be the optimal threshold to rule out myocardial infarction, and our observations suggest this threshold does not provide an acceptable NPV or sensitivity (97.9% [95%CI 96.9-98.7%] and 89.3% [95%CI 84.9-93.5%] respectively). The performance of the ESC pathway is improved by inclusion of a risk stratification threshold and recognition that changes in cardiac troponin concentration within the reference range are important. In a large external validation cohort, we report that more than two-thirds of patients with troponin concentrations above our risk stratification threshold at presentation can be safely ruled out at 3 hours if troponin concentrations are unchanged (<3 ng/L), with no missed diagnosis of type 1 myocardial infarction.

Our findings are consistent with a recently published evaluation of the ESC pathway which reported a negative predictive value of 99.0% [95%CI 98.1-99.5%], and sensitivity of 93.2% [95%CI 87.5-96.8%] in a pooled analysis of five international cohorts.[22] Importantly, this analysis included lower risk patients without ischaemia on the electrocardiogram. In practice, risk stratification and early rule-out pathways are only likely to be applied to patients without

overt myocardial ischaemia on the electrocardiogram.[25] However, interpretation of the electrocardiogram may be subjective and dependent on clinician experience, and therefore we included all patients in our evaluation to ensure our safety estimates were conservative. Likewise, many clinicians use risk stratification tools to identify patients suitable for early discharge. Whilst the ESC guidelines do not advocate use of GRACE score for this purpose, it is widely used and is recommended to guide further investigation in patients whom myocardial infarction has been ruled out. When we restricted our analysis to patients with no significant ST-segment depression or T-wave inversion on the electrocardiogram and GRACE scores of <140, we observed a modest improvement in the NPV of the ESC pathway (98.3% [95% CI, 97.3-99.0%]), although even in this lower risk group the ESC pathway was inferior to the High-STEACS pathway (NPV 99.7% [95% CI, 99.2-99.9%]). Whilst the inclusion of all patients in the primary analysis ensures our safety estimates are conservative, it is important to highlight that in clinical practice, careful clinical assessment and risk assessment is mandatory for all diagnostic pathways. In implementing our pathway, we recommend that patients with overt myocardial ischemia on the electrocardiogram at presentation are admitted for further assessment (Figure S2).

Pickering and colleagues utilized a single diagnostic threshold for myocardial infarction (26 ng/L) in both men and women, although a sensitivity analysis showed the performance of the ESC pathway was similar using sex-specific thresholds.[22] In our analysis, we observed a reduction in the performance of the ESC pathway in men evaluated using the same assay with sex-specific thresholds (34 ng/L in men, 16 ng/L in women; 15 missed events and 5 missed events, respectively). In our sensitivity analysis, use of a single diagnostic threshold of 26 ng/L in men and women did not improve the overall performance of the ESC pathway. In contrast, the

safety of the High-STEACS pathway was robust across both sexes and all pre-specified subgroups of patients. Whilst the use of sex-specific thresholds in pathways that rely on the 99th centile remains contentious in clinical practice, risk stratification thresholds are not influenced by sex,[14] and therefore a single threshold can be applied equally to risk stratify men and women at presentation.

The efficacy of early rule-out pathways is also an important consideration. We demonstrate that the High-STEACS pathway ruled out a higher proportion of patients than the ESC pathway at presentation (40.7% *versus* 28.1%, P<0.001). Whilst our pathway rules out fewer patients at 3 hours (74.2% *versus* 78.9%), P<0.001), of the additional 57 patients ruled out by the ESC pathway, 1 in 5 (22.8%) were incorrectly ruled out and had an index diagnosis of type 1 myocardial infarction identified on subsequent testing. By identifying those patients with a change in cardiac troponin concentration (≥3 ng/L) from presentation to three hours and undertaking further testing, none of these events would be missed by the High-STEACS pathway. This highlights the value of high-sensitivity cardiac troponin assays, which permit the identification of small, but important changes in troponin concentration within the normal reference range, and allow refinement in the risk stratification of patients with suspected acute coronary syndrome. The only disadvantage of our pathway is that in prioritising safety, the specificity and PPV for a diagnosis of myocardial infarction is lower than the ESC pathway at 3 hours (4% and 7% respectively). Specificity is also important, but in our view it need not be prioritized in early rule out pathways. In patients we identify who require hospital admission, the diagnosis of myocardial infarction is best determined by demonstrating a rise and fall in cardiac troponin concentration over 6-12 hours.

The latest ESC guidelines have introduced a one-hour pathway that incorporates a risk stratification step utilising high-sensitivity cardiac troponin concentrations within the reference range.[6] This approach shows promise, and has been validated using both high sensitivity troponin I and high sensitivity troponin T assays, with a NPV of 99.6% [95% CI, 98.4-100] and 99.1% [95% CI, 98.2-99.7%] respectively.[18,19] However, to our knowledge no previous studies have directly compared pathways that utilise a risk stratification step with low cardiac troponin concentrations to those based exclusively on the 99th centile. Further studies are needed to compare the efficacy and safety of retesting at 1 and 3 hours in pathways that incorporate a risk stratification threshold.

One of the limitations of these studies, including our own, is that they are observational in nature, and enrol selected patients rather than all consecutive patients. Indeed, as no patients were discharged on the basis of pathway decisions, the true efficacy and safety of this approach is unknown. The ESC pathway recommends repeat testing in patients who present within 6 hours of symptom onset. Whilst the inclusion of patients who present early is a strength of our study, fewer patients may be ruled out at presentation by the ESC pathway as a consequence. At present, clinicians do not have evidence from prospective randomised controlled trials to inform their practice.[29] As such, we are conducting a multi-centred stepped-wedge cluster randomised trial to determine the efficacy and safety of our pathway **(*Figure S2*)** in unselected consecutive patients across Scotland. The outcome of this trial will help to inform our practice, and provide an evidence base for future recommendations on the use of high-sensitivity cardiac troponins to risk stratify patients with suspected acute coronary syndrome.

Conclusions

The High-STEACS pathway, incorporating low cardiac troponin concentrations to risk stratify patients, rules out more patients on presentation and misses fewer index or recurrent myocardial infarction than guideline-approved pathways based exclusively on the 99th centile. Implementation of this pathway has the potential to improve the efficiency and safety of early rule out approaches for patients with suspected acute coronary syndrome.

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Disclosures

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Table 1. Baseline demographics stratified by cardiac troponin concentration at presentation

	All Patients (n=1,218)	hs-cTnI <5ng/L (n=692)	hs-cTnI ≤99th centile (n=1,002)	hs-cTnI >99th centile (n=216)	P-value
Age	62.36 (14.1)	57.1 (12.3)	60.97 (13.8)	68.78 (14.1)	<0.001
Male (%)	742 (60.9)	383 (55.3)	622 (62.1)	120 (55.6)	0.088
Primary Symptom					
Chest Pain	1044 (85.7)	614 (88.7)	873 (87.1)	171 (79.2)	<0.001
Collapse	13 (1.1)	7 (1.0)	8 (0.8)	5 (2.3)	0.578
Dyspnoea	40 (3.3)	10 (1.4)	25 (2.5)	15 (6.9)	0.151
Palpitations	20 (1.6)	7 (1.0)	15 (1.5)	5 (2.3)	0.043
Symptom onset					
Minutes since onset	208 (116-616)	196 (111-688)	198 (112-594)	249 (130-744)	0.032
< 2 hours (%)	326 (26.8)	196 (28.4)	279 (27.9)	47 (21.8)	0.081
≥ 2 and < 6 hours (%)	463 (38.0)	250 (36.1)	381 (38.0)	82 (38.0)	1.000
≥ 6 hours (%)	429 (35.2)	246 (35.5)	342 (34.1)	87 (40.3)	0.102
Cardiovascular Risk Factors					
Smoker (%)	255 (20.9)	174 (25.1)	217 (21.7)	38 (17.6)	0.385
Diabetes mellitus (%)	184 (15.6)	75 (11)	140 (14.4)	44 (21.0)	0.024
Hypertension (%)	550 (47.2)	255 (38.4)	443 (46.3)	107 (51.4)	0.203
Hyperlipidaemia (%)	493 (43.3)	233 (33.5)	402 (42.9)	91 (44.8)	0.681
Family history (%)	569 (51.5)	350 (53.8)	479 (52.2)	90 (47.9)	0.312
Known angina (%)	409 (34.6)	180 (26.5)	334 (34.2)	75 (36.4)	0.597
Previous MI (%)	308 (26.1)	112 (16.5)	244 (25.2)	64 (30.6)	0.124
Previous PCI (%)	248 (21.3)	110 (16.4)	205 (21.4)	43 (20.9)	0.942
Previous CABG (%)	87 (7.5)	24 (3.9)	71 (7.5)	16 (7.8)	0.995
Heart failure (%)	42 (3.7)	4 (0.6)	25 (2.7)	17 (8.7)	<0.001
Stroke (%)	81 (7.0)	26 (3.9)	63 (6.6)	18 (8.8)	0.337
Peripheral vascular disease (%)	29 (2.6)	7 (1.1)	21 (2.2)	8 (4.0)	0.225
Admission Medication					
Aspirin (%)	442 (38.3)	210 (31.4)	361 (38.0)	81 (39.7)	0.707
Clopidogrel (%)	150 (13.5)	61 (9.5)	119 (13.1)	31 (15.6)	0.409
Warfarin (%)	84 (7.7)	25 (4.0)	66 (7.4)	18 (9.0)	0.52
Beta blocker (%)	353 (31.6)	159 (24.8)	286 (31.2)	67 (33.5)	0.587
ACEi or ARB (%)	379 (33.9)	170 (26.5)	306 (33.3)	73 (36.7)	0.405
CCB (%)	158 (14.4)	72 (11.4)	128 (14.2)	30 (15.2)	0.822
Statin (%)	540 (46.9)	253 (38.4)	444 (46.8)	96 (47.5)	0.91

Values are number (%) or mean (SD) or median (inter-quartile range).
Abbreviations: ACE = angiotensin converting enzyme; ARB = angiotensin receptor blocker; MI = myocardial infarction; CCB = calcium channel blocker; PCI = percutaneous coronary intervention; CABG = coronary artery bypass grafting

Table 2. Diagnostic performance of ESC pathway and High-STEACS pathway for the primary outcome at three hours

		TP	FP	TN	FN	NPV (Mean, 95% CI)	PPV (Mean, 95% CI)	Sensitivity (Mean, 95%CI)	Specificity (Mean, 95%CI)
All patients (n=1,218)	High-STEACS	187	127	900	4	99.5 (99.0-99.9)	59.5 (54.1-64.9)	97.7 (95.5-99.5)	87.6 (85.6-89.6)
	ESC pathway	171	86	941	20	97.9 (96.9-98.7)	66.5 (60.6-72.1)	89.3 (84.9-93.5)	91.6 (89.9-93.3)
Subgroup analysis									
<3 hours since onset (n=544)	High-STEACS	81	60	402	1	99.6 (98.8-100)	57.4 (49.2-65.4)	98.2 (95.3-100)	86.9 (83.8-89.9)
	ESC pathway	73	43	419	9	97.8 (96.2-99.0)	62.8 (53.9-71.3)	88.6 (81.6-94.9)	90.6 (87.9-93.2)
<6 hours since onset (n=789)	High-STEACS	117	98	572	2	99.6 (98.9-99.9)	54.4 (47.7-61.0)	97.9 (95.4-99.9)	85.3 (82.6-88.0)
	ESC pathway	104	66	604	15	97.5 (96.1-98.6)	61.1 (53.7-68.3)	87.1 (81.0-92.8)	90.1 (87.8-92.3)
>6 hours since onset (n=429)	High-STEACS	70	29	328	2	99.2 (98.1-99.9)	70.5 (61.2-79.0)	96.6 (92.4-99.8)	91.8 (88.9-94.5)
	ESC pathway	67	20	337	5	98.4 (96.8-99.4)	76.7 (67.4-84.9)	92.5 (86.4-97.8)	94.3 (91.8-96.6)
Men (n=742)	High-STEACS	122	73	544	3	99.4 (98.5-99.8)	62.5 (55.6-69.1)	97.2 (94.4-99.6)	88.1 (85.5-90.6)
	ESC pathway	110	38	579	15	97.4 (96.0-98.5)	74.2 (66.9-80.8)	87.7 (81.9-93.2)	93.8 (91.8-95.6)
Women (n=476)	High-STEACS	65	54	356	1	99.6 (98.7-100)	54.6 (45.7-63.4)	97.8 (94.2-100)	86.7 (83.4-90.0)
	ESC pathway	61	48	362	5	98.5 (97.0-99.5)	55.9 (46.6-65.0)	91.8 (85.2-97.6)	88.2 (85.0-91.2)
		TP	**FP**	**TN**	**FN**	**NPV (Mean, 95% CI)**	**PPV (Mean, 95% CI)**	**Sensitivity (Mean, 95%CI)**	**Specificity (Mean, 95%CI)**
Subgroup analysis (continued)									
Age <65 years (n=701)	High-STEACS	78	39	583	1	99.7 (99.2-100)	66.5 (57.8-74.7)	98.1 (95.1-100)	93.7 (91.7-95.5)
	ESC pathway	72	29	593	7	98.8 (97.7-99.5)	71.1 (62.0-79.4)	90.6 (84.2-96.5)	95.3 (93.6-96.9)
Age ≥65 years (n=517)	High-STEACS	109	88	317	3	98.9 (97.5-99.7)	55.3 (48.4-62.2)	96.9 (93.7-99.5)	78.2 (74.2-82.2)
	ESC pathway	99	57	348	13	96.3 (94.1-98.0)	63.4 (55.7-70.7)	88.1 (82.0-93.7)	85.8 (82.4-89.2)
	High-STEACS	85	77	352	4	98.7 (97.4-99.6)	52.5 (44.8-60.1)	90.5 (90.5-98.9)	82.0 (78.3-85.6)

Known ischaemic heart disease (n=518)	ESC pathway	73	52	377	16	95.8 (93.6-97.6)	58.3 (49.6-66.8)	81.7 (73.6-89.3)	87.8 (84.7-90.8)
No known ischaemic heart disease (n=680)	High-STEACS	99	48	533	0	99.9 (99.6-100)	67.2 (59.5-74.5)	99.5 (98.1-100)	91.7 (89.4-93.9)
	ESC pathway	95	33	548	4	99.2 (98.3-99.8)	74.0 (66.2-81.2)	95.5 (91.4-99.0)	94.2 (92.3-96.1)

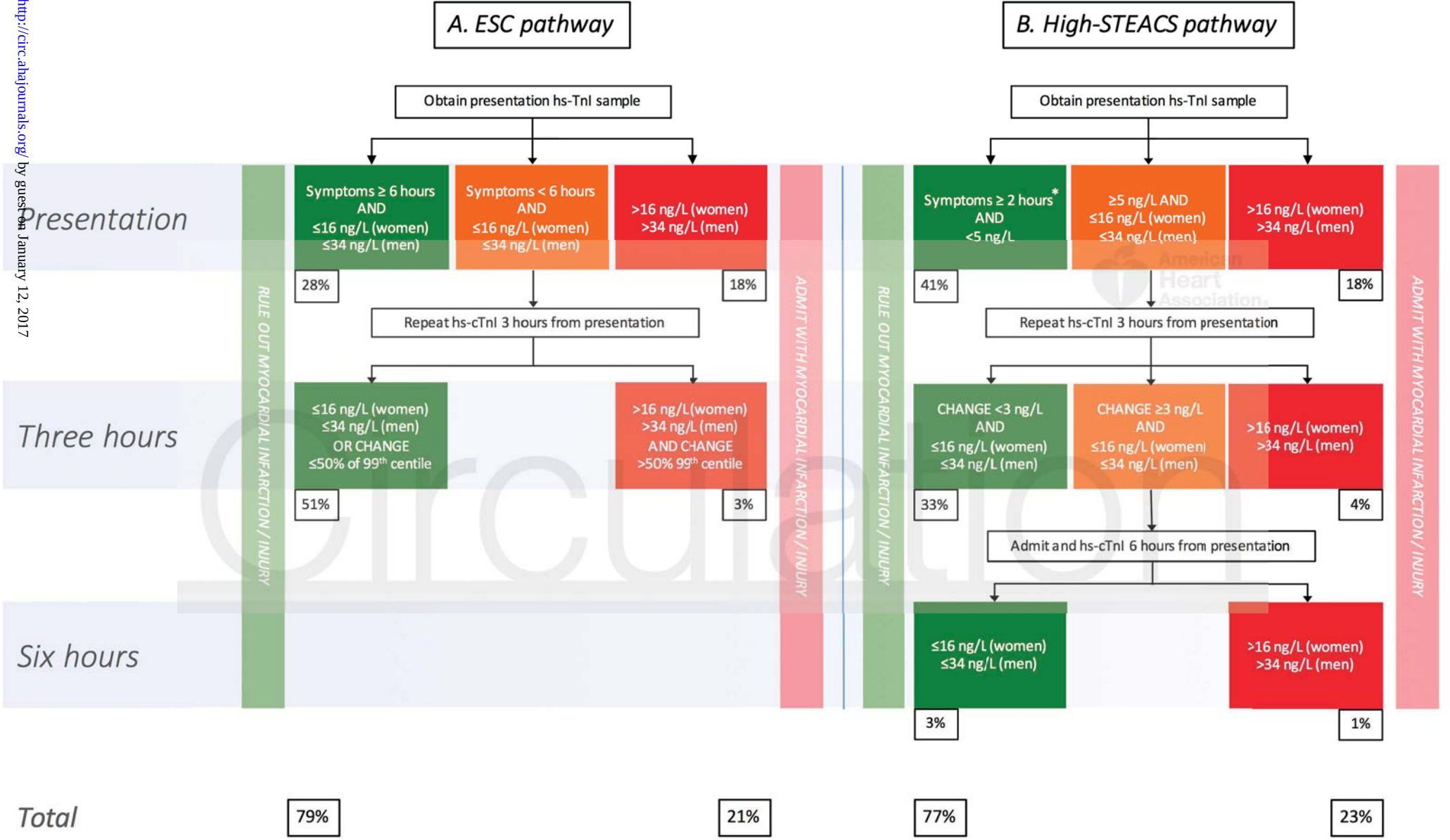
Abbreviations: TP = True Positive, FP = False Positive, TN = True Negative, FN = False Negative, NPV = Negative Predictive Value, PPV = positive predictive value

Figure Legends

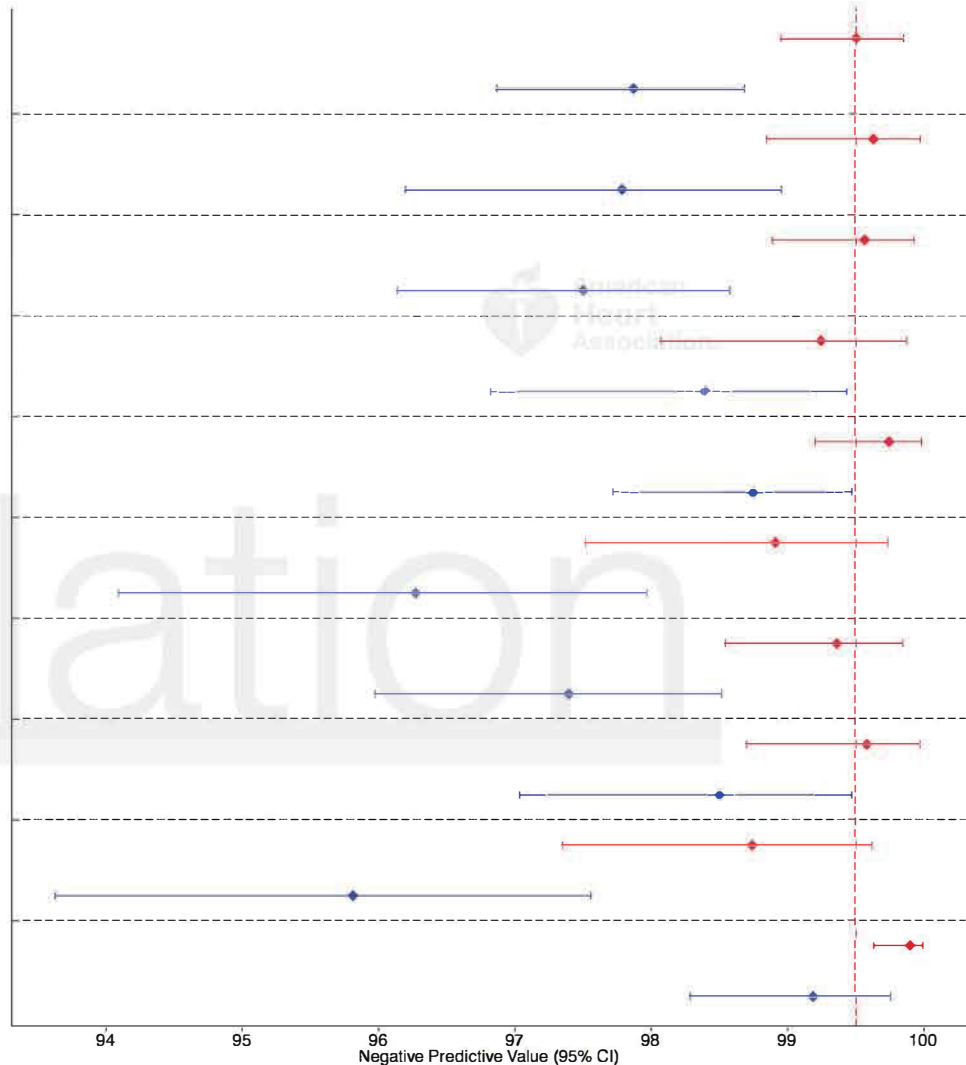
Figure 1. Summary of the ESC (A) and High-STEACS (B) rule out pathways for myocardial infarction. Percentages indicate number of patients ruled in or out at a given time point, as a proportion of the analysis population (n=1,218).

*In the High-STEACS pathway, patients with cardiac troponin concentrations <5 ng/L who present within two hours of symptom onset are retested at three hours.

Figure 2. Negative predictive value for index type 1 myocardial infarction, or myocardial infarction or cardiac death at 30 days of conventional and High-STEACS pathways. Forest plot of the negative predictive value and 95% confidence intervals of the High-STEACS pathway (red) and the ESC pathway (blue) stratified by pre-specified subgroups. Numbers are true negative, false negative and negative predictive value (95% confidence intervals). The vertical dashed line (red) highlights the central estimate of the negative predictive value of the High-STEACS pathway in the total population.



		TN	FN	NPV (95% CI)
All	High−STEACS Pathway	900	4	99.5 (99–99.9)
	ESC Pathway	941	20	97.9 (96.9–98.7)
Symptoms (hrs)	Less than three	402	1	99.6 (98.8–100)
		419	9	97.8 (96.2–99)
	Less than six	572	2	99.6 (98.9–99.9)
		604	15	97.5 (96.1–98.6)
	Over six	328	2	99.2 (98.1–99.9)
		337	5	98.4 (96.8–99.4)
Age	Less than 65	583	1	99.7 (99.2–100)
		593	7	98.8 (97.7–99.5)
	Over 65	317	3	98.9 (97.5–99.7)
		348	13	96.3 (94.1–98)
Sex	Male	544	3	99.4 (98.5–99.8)
		579	15	97.4 (96–98.5)
	Female	356	1	99.6 (98.7–100)
		362	5	98.5 (97–99.5)
Ischaemic Heart Disease	Yes	352	4	98.7 (97.4–99.6)
		377	16	95.8 (93.6–97.6)
	No	533	0	99.9 (99.6–100)
		548	4	99.2 (98.3–99.8)



Comparison of the Efficacy and Safety of Early Rule Out Pathways for Acute Myocardial Infarction

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SUPPLEMENTAL MATERIAL

Comparison of the efficacy and safety of early rule out pathways for acute myocardial infarction

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Tables and Figures: 8

Table S1 – Baseline characteristics for the APACE external validation cohort

	APACE Study* (n=2,533)
Age	61 (16.0)
Male (%)	1,722 (68.0)
Primary Symptom	
Chest Pain	2,214 (87.4)
Symptom onset	
Minutes since onset	300 (120-720)
Less than three hours (%)	717 (28.5)
Less than six hours (%)	1,338 (53.2)
Over six hours (%)	1,054 (41.9)
Cardiovascular Risk Factors	
Smoker (%)	635 (25.1)
Diabetes mellitus (%)	451 (17.8)
Hypertension (%)	1,591 (62.8)
Hyperlipidaemia (%)	1,293 (51.0)
Family history (%)	987 (40.9)
Known angina (%)	883 (34.9)
Previous MI (%)	621 (24.5)
Previous PCI (%)	646 (25.5)
Previous CABG (%)	228 (9.0)
Stroke (%)	149 (5.9)
Peripheral vascular disease (%)	146 (5.8)
Troponin concentration at presentation	
<5 ng/L (%)	1,348 (53.2)
≥5 ng/L and ≤ 99th centile (%)	735 (29.0)
>99th centile (%)	450 (17.8)
Adjudicated Diagnosis	
Type 1 myocardial infarction (%)	289 (11.4)
All myocardial infarction (%)	378 (14.9)

**The APACE study is a prospective cohort study of patients with suspected acute coronary syndrome presenting to the Emergency Department of Basel and six other centers in Europe between April 2006 and August 2015. Blood samples were obtained on presentation and at 3, and 6h for high-sensitivity cardiac troponin I testing. All diagnoses were adjudicated by two independent cardiologists; the diagnosis of type 1 myocardial infarction required at least one high-sensitivity cardiac troponin I concentration above the sex-specific 99th centile upper reference limit (16 ng/L women, 34 ng/L men). This study was approved by the local ethics committee.*

Table S2. Patients ruled out by the ESC pathway at 0 and 3 hours meeting the primary outcome

Age	Gender	Time since symptom onset (Minutes)	Troponin concentration, ng/L (hours)	Relative Change (%)	Absolute Change	Presenting Symptom	Index Diagnosis	Risk Factors	Initial ECG	Management
81	Male	444	31 (0) 33 (3) 39 (12)	6.5	2	Chest Pain	Type 1 MI	Hypertension Hyperlipidaemia Ischaemic Heart Disease Previous CABG	Sinus Rhythm ST Depression T wave Inversion	PCI to LCx
57	Male	440	33 (0) 80 (3) 144 (5)	142.4	47	Chest Pain	Type 1 MI	Previous Smoker Family History of CHD	Sinus Rhythm	PCI to OM1
70	Male	375	17 (0) 160 (3) 2583 (6)	841.2	143	Chest Pain	Type 1 MI	Previous Smoker Diabetes Hypertension Hyperlipidaemia Previous MI	Sinus Rhythm RBBB	Medical
84	Male	4900	25 (0) 44 (3)	76.0	19	Chest Pain	Type 1 MI	Hypertension Previous MI Previous PCI Previous CABG Previous Stroke	Atrial Fibrillation	PCI to SVG-D1
82	Female	86	11 (0) 15 (3) 26 (10)	36.4	4	Chest Pain	Type 1 MI	Hypertension	Sinus Rhythm	Medical
62	Male	70	27 (0) 32 (3) 50 (11)	18.5	5	Chest Pain	Type 1 MI	Current Smoker Diabetes Hypertension Hyperlipidaemia Previous MI Previous PCI	Sinus Rhythm	Medical
87	Male	139	5 (0) 16 (3) 691 (10)	220.0	11	Chest Pain	Type 1 MI	Previous Smoker Hypertension Ischaemic Heart Disease Previous CABG	Atrial Fibrillation ST Depression	Medical

73	Male	180	26 (0) 29 (3) 41 (9)	11.5	3	Chest Pain	Type 1 MI	Previous Smoker Hypertension Hyperlipidaemia Family history of CHD Previous MI Previous CABG	Sinus Rhythm LBBB	Medical
58	Male	122	26 (0) 33 (3) 46 (11)	26.9	7	Dyspnoea	Type 1 MI	Previous Smoker Diabetes Family history of CHD Ischaemic Heart Disease Previous MI Previous CABG Previous Stroke	Sinus Rhythm T wave inversion	Medical
63	Female	151	10 (0) 16 (3) 167 (10)	60.0	6	Chest Pain	Type 1 MI	Current Smoker Family history of CHD	Sinus Rhythm ST Depression	PCI to LAD
66	Male	89	12 (0) 31 (3) 202 (10)	158.3	19	Chest Pain	Type 1 MI	Hypertension Previous MI Previous PCI	Sinus Rhythm	Medical
60	Male	81	2 (0) 6 (3) 2932 (11)	200.0	4	Chest Pain	Type 1 MI	Current Smoker Family History of CHD Ischaemic Heart Disease Previous PCI	Sinus Rhythm T wave inversion (old)	PCI to RCA/D1
56	Male	262	8 (0) 14 (3) 307 (10)	75.0	6	Chest Pain	Type 1 MI	Previous Smoker Hypertension Hyperlipidaemia Family history of CHD Ischaemic Heart Disease Previous MI Previous PCI	Sinus Rhythm	Medical
77	Male	272	21 (0) 26 (3) 56 (10)	23.8	5	Chest Pain	Type 1 MI	Previous Smoker Diabetes Hypertension Hyperlipidaemia Family history of CHD Previous MI Previous PCI	Atrial Fibrillation Inferior Q waves	Medical
66	Male	305	22 (0) 36 (3)	63.6	14	Chest Pain	Type 1 MI	Ischaemic Heart Disease Hypertension	Sinus Rhythm Bradycardia	PCI to LCx Instent Restenosis

			50 (8)					Hyperlipidaemia Previous MI Previous PCI		
60	Male	295	14 (0) 14 (3) 170 (8)	0	0	Chest Pain	Type 1 MI	Current Smoker Hypertension Hyperlipidaemia Family history of CHD Ischaemic heart disease Previous MI	Sinus Rhythm Bradycardia	Angiography 70% stenosis OM1 Medical
88	Female	222	15 (0) 19 (3)	26.7	4	Chest Pain	Type 1 MI	Ischaemic heart disease Previous MI Previous PCI Family history of CHD	Sinus Rhythm	Medical
89	Female	165	16 (0) 18 (3) 24 (10)	12.5	2	Chest Pain	Type 1 MI	Hypertension Family history of CHD Ischaemic Heart Disease	Sinus Rhythm	Medical
82	Male	126	19 (0) 20 (3) 22 (11) Re-attendance 52 (0) 44 (3) 24 (10)	5.3	1	Chest Pain	Musculoskeletal Chest Pain	Previous Smoker Diabetes Hyperlipidaemia Family history of CHD Ischaemic Heart Disease Previous MI Previous CABG	Sinus Rhythm First Degree HB Left Axis Deviation RBBB	Re-presented with ongoing chest pain two days post index presentation Missed Type 1 MI
73	Female	425	9 (0) 11 (3)	22.2	2	Chest Pain	Paroxysmal AF	Previous Smoker Hypertension Hyperlipidaemia Ischaemic Heart Disease Previous MI Previous PCI	Atrial Fibrillation RBBB T wave inversion	Re-presented with inferior STEMI 14 days post index presentation PCI to RCA Type 1 MI

Demarcations for missed index events with ≥6 hours symptoms (n=4), <6 hours symptoms (n=14) and 30 day events (n=2)
AF = atrial fibrillation, CABG = coronary artery bypass graft, CHD = coronary heart disease, LBBB = left bundle branch block, RBBB = right bundle branch block, MI = myocardial infarction, PCI = percutaneous coronary intervention, STEMI = ST-segment elevation myocardial infarction.

Table S3. Patients ruled out by the High-STEACS pathway at 0 and 3 hours meeting the primary outcome

Age	Gender	Time since symptom onset (Minutes)	Troponin concentration, ng/L (hours)	Relative Change (%)	Absolute Change	Presenting Symptom	Index Diagnosis	Risk Factors	Initial ECG	Management
81	Male	444	31 (0) 33 (3) 39 (12)	6.45	2	Chest Pain	Type 1 MI	Hypertension Hyperlipidaemia Ischaemic Heart Disease Previous CABG	Sinus Rhythm ST Depression T wave Inversion	PCI to LCx
60	Male	295	14 (0) 14 (3) 170 (8)	0	0	Chest Pain	Type 1 MI	Current Smoker Hypertension Hyperlipidaemia Family history of CHD Ischaemic heart disease Previous MI	Sinus Rhythm Bradycardia	Angiography 70% stenosis OM1 Medical
82	Male	126	19 (0) 20 (3) 22 (11) Re-attendance 52 (0) 44 (3) 24 (10)	5.3	1	Chest Pain	Musculoskeletal Chest Pain	Previous Smoker Diabetes Hyperlipidaemia Family history of CHD Ischaemic Heart Disease Previous MI Previous CABG	Sinus Rhythm First Degree HB Left Axis Deviation RBBB	Re-presented with ongoing chest pain two days post index presentation Missed Type 1 MI
73	Female	425	9 (0) 11 (3)	22.2	2	Chest Pain	Paroxysmal AF	Previous Smoker Hypertension Hyperlipidaemia Ischaemic Heart Disease Previous MI Previous PCI	Atrial Fibrillation RBBB T wave inversion	Re-presented with inferior STEMI 14 days post index presentation PCI to RCA Type 1 MI

Demarcation for missed index events (n=2) and 30 day events (n=2)

AF = atrial fibrillation, CABG = coronary artery bypass graft, CHD = coronary heart disease, LBBB = left bundle branch block, RBBB = right bundle branch block, MI = myocardial infarction, PCI = percutaneous coronary intervention. STEMI = ST-segment elevation myocardial infarctioz

Table S4 – 2x2 table for internal validation of delta criteria at three hours

	Type 1 MI	No Type 1 MI
Change ≥3 ng/L at 3 hours	40	52
Change <3 ng/L at 3 hours	2	216

Patients with cardiac troponin concentrations ≥5 ng/L and <99th centile on presentation are re-tested at three hours. Those with a change in cardiac troponin of <3 ng/L are ruled out if they remain <99th centile.

Table S5 – 2x2 table for external validation of delta criteria at three hours

	Type 1 MI	No Type 1 MI
Change ≥3 ng/L at 3 hours	51	170
Change <3 ng/L at 3 hours	0	514

Patients with cardiac troponin concentrations ≥5 ng/L and <99th centile on presentation are re-tested at three hours. Those with a change in cardiac troponin of <3 ng/L are ruled out if they remain <99th centile.

Table S6 – 2x2 table with diagnostic performance of the High-STEACS pathway at 6 hours

	Type 1 MI	No Type 1 MI
Pathway rules in	187	88
Pathway rules out	4	939

Patients with cardiac troponin concentrations <5 ng/L who present over two hours from time of symptom onset are ruled out on presentation. Those ≥5 ng/L and <99th centile on presentation, and those who present within two hours of symptom onset are re-tested at three hours. Those with a change in cardiac troponin of <3 ng/L are ruled out if they remain <99th centile, with all other patients admitted for peak testing at six hours.

Figure S1. Study population, adjudicated diagnosis and 30 day outcomes

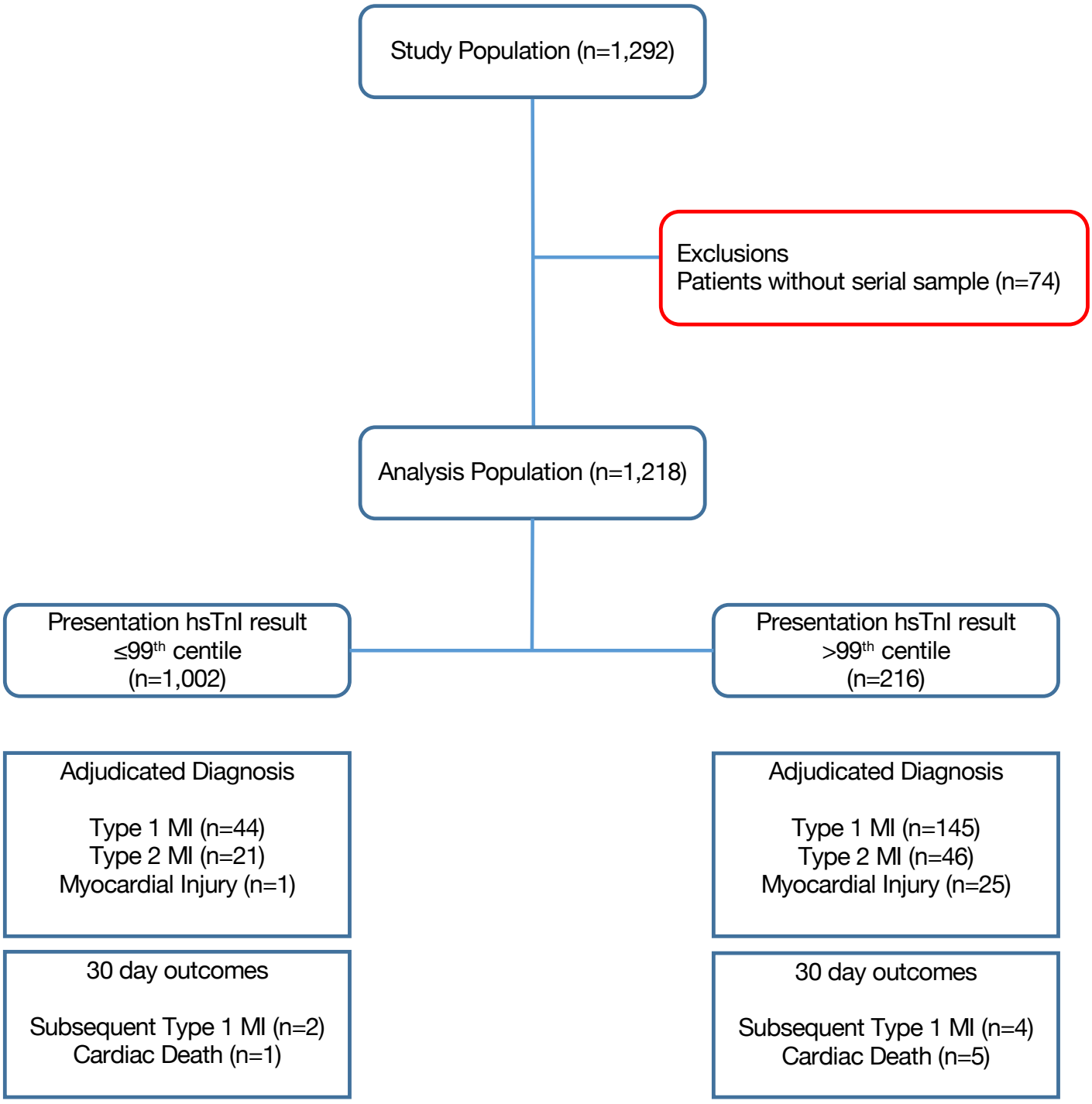
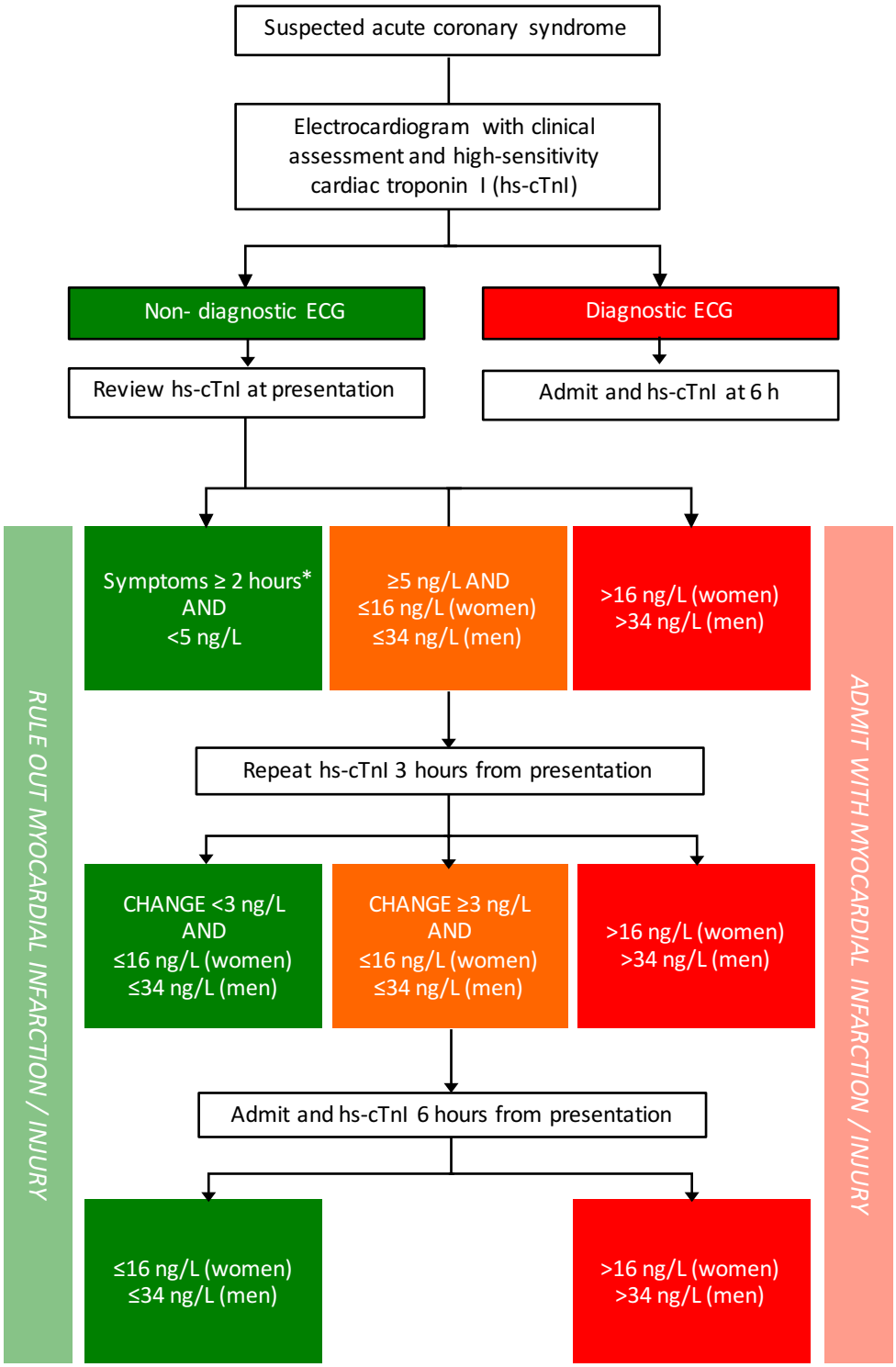


Figure S2. Diagnostic algorithm of the High-STEACS pathway



*Diagnostic algorithm of the High-STEACS pathway, currently being evaluated as part of a multi-centre stepped-wedge cluster randomised trial in unselected consecutive patients across Scotland. *In the High-STEACS pathway, patients with cardiac troponin concentrations <5 ng/L who present within two hours of symptom onset are retested at three hours.*